Remarks

Claims 1-6, 8, 9, and 39-42 are pending in the subject application and currently before the Examiner. By this Amendment, Applicants have added new claim 43. Support for the new claim can be found throughout the subject specification. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-6, 8, 9, and 39-43 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 1-6, 8, 9, and 39-42 are rejected under 35 USC §112, first paragraph, as nonenabled by the subject specification. Applicants note that the Examiner acknowledges that the specification enables methods of inhibiting intimal hyperplasia at a site in a blood vessel by periadventitial administration of a DNA expression vector encoding VEGF. However, the Examiner asserts that the specification does not enable treatment of vascular disorders in any species other than a rabbit. Applicants respectfully traverse this ground of rejection.

Under this rejection, the Examiner has indicated that claims 39-42, which were newly added by Applicants' Amendment dated July 26, 2004, are not enabled for the same grounds as applied to claims 1-6, 8, and 9. The Examiner asserts that the specification does not disclose any purpose for the method of claims 39-42 other than for treatment or prevention of stenosis or restenosis. It is well settled in patent law that a specification need not explicitly disclose those uses which would be obvious to a person of ordinary skill in the art. In the instant case, an ordinarily skilled artisan would know that the method could be used for purposes including, but not limited to, studying activity of VEGF on the cells of the blood vessel. Such use fully satisfies the utility requirement under 35 USC §101 and the "how to use" requirement under 35 USC §112, first paragraph. Accordingly, Applicants respectfully assert that claims 39-42 are fully enabled by the subject specification.

The Examiner maintains that small animal models of intimal hyperplasia disease and treatment are not predictive of success in other animals, particularly humans. Applicants respectfully maintain that the rabbit model, and other small animal models, is suitable to provide evidence of enablement of the claimed method in humans and other large mammals. The Examiner has cited several references to suggest that small animal models do not provide results that extrapolate to humans. However, the U.S. Food and Drug Administration (FDA) considers such animal models in evaluating whether a new drug or therapy can move forward for clinical testing in humans. Thus, it

appears that animal models which are accepted by the FDA are not acceptable by the U.S. Patent Office. The courts have repeatedly indicated that the U.S. Patent Office is not to place itself in the role of the FDA and evaluate the safety and efficacy of a drug or therapy. The enablement standard is a much lower threshold than the levels required by the FDA for safety and efficacy. Yet, as Applicants have repeatedly indicated, the FDA has granted approval to Applicants to conduct human clinical trials with their invention. Moreover, the FDA has granted approval to Applicants to proceed from phase I into phase II clinical trials. Thus, the FDA, which also reviewed Applicants small animal model data, was of the opinion that the data from animal models using Applicants' therapeutic methods showed sufficient promise to warrant approval for human trials. One can assume that the FDA found Applicants' small animal data as being "reasonably predictive" of efficacy in humans. In contrast, the Patent Office has maintained that a person of ordinary skill in the art would be unable to practice the invention on humans or other large animals.

The Examiner indicates in the last sentence on page six of the Office Action that the Muller *et al.* reference indicates that "results in one animal model are not necessarily predictive of results in another animal model . . .." While this may be the opinion of the authors of the cited reference, U.S. patent law does not require that the results in an animal model are "necessarily predictive" of results in another. *In vivo* data from animal models is not even necessarily required to satisfy the enablement requirement for a therapeutic method claim. The Examiner also quotes the Muller *et al.* reference as stating that "a pharmacological therapy that is effective in one animal model may be ineffective in another species or in humans." (emphasis added). Note that Muller *et al.* does not say that the therapy will be ineffective; the authors only state that the therapy might not be effective, which can also be read as indicating that the therapy might be effective. Applicants note that Muller *et al.* also state that "Ideally, promising new drug therapies should be proved effective in several animal models . . ." before human trials are performed. As the Examiner is aware, Applicants have shown just what the Muller *et al.* authors asked for (and what the FDA accepted), *i.e.*, efficacy of the claimed invention in multiple animal models.

In regard to the Lafont *et al.* reference cited by the Examiner, Applicants note that it was published in 1995 and, therefore, does not represent (nor does the Muller *et al.* reference) the state of the art with respect to the relationship between small animal models and humans in the treatment of

intimal hyperplasia. It is further noted that the title of the Lafont *et al.* reference is "Why do Animal Models of Post-Angioplasty Restenosis Sometimes Poorly Predict the Outcome of Clinical Trials?" (emphasis added). Thus, it is clear from the title that the authors are not suggesting that animal models are always poor predictors of results in humans, but rather that they sometimes are poor predictors. From the title alone, one would not conclude that the reference establishes that animal models cannot be used to reasonably predict success in human trials.

Applicants also respectfully assert that the Patent Office has recognized that small animal models are reasonably predictive of outcome in human clinical trials. U.S. Patent No. 5,830,879 issued to Isner in 1998 with claims directed to methods of inducing reendothelialization of an injured blood vessel of a human. The only data presented in the Isner patent was obtained using rabbits. As the Examiner is aware, an issued U.S. patent is presumed to be valid, including in regard to enablement.

Thus, Applicants respectfully assert that the references cited by the Examiner do not negate Applicants' assertion that the small animal models used with the claimed invention are "reasonably predictive" of efficacy in humans.

In finding unpersuasive the Declaration under 37 CFR §1.132 by John Martin, M.D. that has been submitted in the subject application, and the report by Applicants of additional positive results in human clinical trials, the Examiner indicates in the instant Office Action that the subject specification only discloses VEGF-A (and isoforms thereof) whereas the data described in the Declaration was obtained using VEGF-D. Applicants note that the claimed invention is not limited to VEGF-A or VEGF-D. The subject specification contemplates that the agent used in the claimed method can be any agent that is an agonist of a Flt-1 or a Flk-1 receptor. The subject specification does not limit VEGF to VEGF-A and contemplates the use of any VEGF or compound that exhibits VEGF-like biological activity. Applicants respectfully assert that a person of ordinary skill in the art, having the benefit of the teachings of the subject specification, would expect that VEGF-A and VEGF-D could both be used in the claimed methods.

The Examiner also states in regard to the data presented in Dr. Martin's Declaration that it "provided no statistical analysis of the results, the sample size was small, and the results indicated that the treatment may in fact increase intimal hyperplasia over time." All of these issues are

irrelevant to the issue of enablement. Satisfaction of the enablement requirement does not require statistical analysis or a certain sample size for the data. Nor does it matter that a disease condition may reoccur over time. A treatment for cancer is still a treatment even if the treatment only results in remission for a limited amount of time. Similarly, it is of no consequence that a treatment reduces intimal hyperplasia, even if for only one day, if the treatment does reduce intimal hyperplasia for that one day.

In view of the above remarks, reconsideration and withdrawal of the rejection under 35 USC§112, first paragraph, is respectfully requested.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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